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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,069	BRASLAWSKY ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/9/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-19, 35 and 41-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-34 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-50 are pending.

2. Applicant's election with traverse of the Invention of Group IV, claims 29-34, 36-40 and 20-28 in the Paper filed 6/9/2004 is acknowledged. The traversal is on the grounds that the dimeric antibodies of the instant invention are all structurally modified (i.e., CH2 deleted) in the constant region and this structural modification is independent of the antibodies antigen specificity and can be regarded as generic in nature. The traversal also states that the MPEP (803.2) states that if the members of a Markush group are sufficiently few in number or so closely related that search and examination of the entire claim could be made without serious burden, the examiner must examine all of the members of the Markush Group, even though they are independent and distinct inventions. The traversal further states that the search and examination of the full Markush group consisting of the tetravalent antibody dimers would be no greater burden on the examiner than if the search and examination is restricted to a dimeric antibody having single antigen specificity. This is not found persuasive. The Inventions are distinct because as stated in the restriction requirement the dimeric antibodies of the instant invention are all structurally and functionally distinct in that they have different sequences and different antigen specificities. Thus, the instantly claimed antibodies are completely unrelated and require different searches. Applicant is reminded that restriction to one of two or more inventions in an application is proper under the statute

if they are able to support separate patents and they are either independent or distinct. The instantly claimed dimeric antibodies all having different antigen specificities would support separate patents because an antibody that binds CD2 would not read on a patent issued to an antibody that binds TAG-72. It is noted that numerous issued U.S. Patents are drawn to antibodies, all of which share a common, generic structure (i.e., two identical heavy chains and two identical light chains), but differ only in sequence and antigen specificity. With respect to burden of search, the search for each of the dimeric antibodies is not co-extensive particularly with regard to the literature search. A reference, which would anticipate or render obvious an anti-CD2 antibody would not necessarily anticipate or render obvious an anti-TAG-72 antibody, for example. Thus, the literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and different patentability issues are involved in the examination of each group. The Examiner notes that rejoinder of process claims that depend from or otherwise include all the limitations of the allowable product claims will be considered for rejoinder in accordance with the provisions of MPEP § 821.04 once allowable subject matter has been identified in the product claims under examination.

For these reasons the restriction requirement is deemed to be proper and is made FINAL.

3. Claims 1-19, 35 and 41-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 20-34 and 36-40 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

a. The priority information on the first line of the specification should be amended to contain, a reference to each such prior-filed provisional application number. No relationship should be specified whenever a claim for the benefit of a provisional application under 35 U.S.C 119(e) is made and no provisional application may claim benefit to another provisional application. Thus, Applicant should delete the "which is a continuation-in-part" statement at page 1, line 6 of the specification.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

b. Applicant is required to update the USSNs in the specification that have now issued as U.S. Patents. See page 14, line 18 and page 33, line 9. Applicant is reminded to check the entire specification and update all USSNs that have now issued as U.S. Patents with the respective U.S. Patent number. Additionally, the status of USSN 09/259,338 at page 45, line 28 needs to be updated as "now abandoned".

Appropriate correction is required.

Claim Objections

6. Claim 37 is objected to because of the following informalities:

Claim 37 is objected to as being drawn to non-elected inventions.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 21-34 and 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 22-24 and 30-32 are indefinite in the recitation of "modified" in claims 22-24 and 30-32 because the claims do not state the function, which is to be achieved. The term "modified" is relative in nature, which renders the claims indefinite since it encompasses many different amino acid sequences as well as many different forms and modifications and it is not clear from the disclosure at page 8, which particular "modified" attribute is being referred to. The term "modified" is not defined by the claims; the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, and one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

b. Claims 21-34 and 36-40 are indefinite for reciting "monomeric subunit" in claims 21, 22, 26, 29 and 30. The phrase "monomeric subunit" is unclear because it is not defined by the claims and the phrase has not been adequately defined by the specification. Does the phrase "monomeric subunit" mean a single VH domain or a single VL domain or is the "monomeric subunit" a polypeptide chain comprising multiple VH and VL domains (i.e., $(V_L)_1$-$(V_H)_1$-$(V_L)_2$-$(V_H)_2$)? What is a "monomeric subunit" required by the claims?

c. Claims 22-26 and 30-33 are indefinite for reciting "monomeric subunit comprises a modified antibody" in claims 22 and 30. Because a dimeric antibody by definition consists of two simpler molecules (i.e., monomeric subunits), it is unclear what is meant by the phrase "monomeric subunit comprises a modified antibody". Does the modified antibody comprise at least one modified monomeric subunit or does the monomeric subunit comprise a modified antibody? Does one of the polypeptide chains (i.e., monomeric subunit) comprise a larger modified antibody molecule and what does the monomeric subunit comprising a modified antibody look like?

d. Claims 27 and 34 are indefinite for reciting "dimeric antibody comprises a homodimer". By definition a "dimeric" antibody consists of two identical simpler polypeptide chains (i.e., $(V_L)_1$-$(V_H)_1$-$(V_L)_2$-$(V_H)_2$), thus, it is unclear what is contemplated by the phrase "dimeric antibody comprises a homodimer". Does the dimeric antibody consist of two identical polypeptide chains or are additional polypeptide chains contemplated by the phrase? Further, is the dimeric antibody a homodimer in

that it comprises two identical monomeric subunits or two identical polypeptide chains or two identical antigen specificities?

e. Claim 28 is indefinite for reciting "dimeric antibody comprises a heterodimer". Again, by definition a "dimeric" antibody consists of two simpler molecules, thus, it is unclear what is contemplated by the phrase "dimeric antibody comprises a heterodimer". First, does the dimeric antibody consist of two polypeptide chains (i.e., a dimer) or are additional polypeptide chains contemplated by the phrase? Second, if the first polypeptide chain of the dimeric antibody consists of $(V_L)_1$-$(V_H)_1$-$(V_L)_2$-$(V_H)_2$), for example, what is the second polypeptide chain of the dimeric antibody such that the dimeric antibody comprises a heterodimer? Further, is the dimeric antibody a heterodimer in that it comprises two different monomeric subunits or two different polypeptide chains or two different antigen specificities?

f. Claims 38-40 are indefinite for reciting "associated" in claim 38 as it is not clear in what manner the association occurs. Is the cytotoxic agent non-covalently "associated" with the dimeric antibody or is the cytotoxic agent actually linked or conjugated to the dimeric antibody? Further, it is unclear if the cytotoxic agent is "associated" with the variable region or the constant region or the hinge region?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20-24, 26-32, 34 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a dimeric antibody comprising two polypeptide chains having both VH and VL domains (i.e., monomeric subunits), wherein the dimeric antibody comprises 6 CDRs, three from the VH domain and three from the VL domain and wherein the dimeric antibody binds antigen, does not reasonably provide enablement for a dimeric antibody comprising two polypeptide chains that do not contain a full set of 6 CDRs from the VH and the VL domains and do not bind antigen as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 20-24, 26-32, 34 and 38-40 are broadly drawn to a dimeric antibody and a kit comprising a dimeric antibody comprising a plurality of monomeric subunits that are non-covalently associated, wherein the dimeric antibody is a domain-deleted antibody. Thus, the claims encompass dimeric antibodies comprising deletion of the VH

domain or the VL domain or both VH and VL domains, wherein the dimeric antibody would not comprise a full set of 6 CDRs from the VH and the VL domains and would not bind antigen.

The specification discloses only dimeric antibodies that comprise both a VH and a VL chain (i.e., H_2L_2 and H_4L_4) and the dimeric antibodies bind antigen (see Examples). Additionally, the specification teaches that the VL and VH domains of an antibody combine to form the variable region that defines a three-dimensional antigen binding site and the antigen binding site is defined by three complementary determining regions (CDRs) on each of the VH and VL chains (see page 20, lines 15-22). The specification does not enable dimeric antibodies comprising a plurality of just any monomeric subunits, wherein just any domain has been deleted such that the dimeric antibody does not contain both VH and VL domains (all six CDRs) and does not bind antigen. Further, the claims do not state/require that the dimeric antibody binds antigen.

The claims encompass dimeric antibody and a kit comprising a dimeric antibody comprising a plurality of monomeric subunits that are non-covalently associated, wherein the dimeric antibody is a domain deleted antibody, which does not contain a full set of 6 CDRs form both the VH and VL chains and does not bind antigen. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light

chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al(Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the dimeric antibody as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using a dimeric antibody containing fewer than 6 CDRs, resulting in a dimeric antibody that does not bind antigen.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a domain deleted dimeric antibody. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 29-34 and 36-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Goel et al [a] (Cancer Research, 60:6964-6971, December 15, 2000, Ids reference XR).

Claims 29-34 and 36-40 are interpreted as being drawn to a dimeric antibody comprising a plurality of monomeric subunits that are non-covalently associated, wherein the dimeric antibody is a CH2 domain deleted dimeric antibody, and is a homodimer and binds the TAG-72 tumor antigen and the antibody is labeled (i.e., linked or conjugated) with a radioisotope. Claim 30 is interpreted as being drawn to a dimeric antibody wherein at least one monomeric subunit is modified. Further, the phrase "monomeric subunit(s)" is interpreted as a single polypeptide chain.

Goel et al [a] teach a tetravalent scFv that was formed by the noncovalent association of the covalent dimer $sc(Fv)_2$ (i.e., homodimer comprising two identical scFv polypeptide chains; plurality of monomeric subunits) and the antibody is modified and has at least a portion of one constant region domain omitted and lacks a CH2 domain

(see Figure 1). Goel et al [a] teach that the tetravalent scFv antibody binds the TAG-72 tumor antigen (see 6968, left column) and the dimeric antibody is labeled with ^{125}I or ^{131}I (see page 6965, left column).

12. Claims 29-34 and 36-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Goel et al [b] (Journal of Biochemistry, 127:829-836, May 2000).

The claims and their interpretation have been described supra.

Goel et al [b] teach CC49 scFvs that were expressed as a noncovalent dimer ($[scFv]_2$-His_6) that binds the TAG-72 tumor antigen (see abstract and page 831, right column). Thus, the dimeric antibody taught by Goel et al [b] is a homodimer (i.e., two identical polypeptide chains; CC49 $[scFv]_2$-His_6) comprising a plurality of monomeric subunits that non-covalently associate (interpreted as two identical polypeptide chains that noncovalently associate) and the CC49 $(scFv)_2$-His_6 is modified and has at least a portion of one constant region domain omitted (i.e., domain deleted) and lacks a CH2 domain. Goel et al [b] teach that the CC49 $(scFv)_2$-His_6 is labeled with ^{125}I or ^{131}I (see page 830, right column).

13. Claims 29-34 and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavlinkova et al [a] (The Journal of Nuclear Medicine, 40(9):1536-1546, September 1999).

The claims and their interpretation have been described supra.

Pavlinkova et al [a] teach CC49 scFvs that were expressed as a stable noncovalent dimer (CC49 $[scFv]_2$) that binds the TAG-72 tumor antigen (see abstract and page 1537, left column). Thus, the dimeric antibody taught by Pavlinkova et al [a] is a homodimer (i.e., two identical polypeptide chains; [CC49 $scFv]_2$) comprising a plurality of monomeric subunits that non-covalently associate (interpreted as two identical polypeptide chains that noncovalently associate) and the CC49 $(scFv)_2$ is modified and has at least a portion of one constant region domain omitted (i.e., domain deleted) and lacks a CH2 domain. Pavlinkova et al [a] teach that the CC49 $(scFv)_2$ is labeled with ^{125}I or ^{131}I (see page 1537, right column).

14. Claims 29-34 and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavlinkova et al [b] (Clinical Cancer Research, 5:2613-2619, September 1999).

The claims and their interpretation have been described supra.

Pavlinkova et al [b] teach CC49 scFvs that were expressed as a stable noncovalent dimer (CC49 $[scFv]_2$) that binds the TAG-72 tumor antigen (see abstract and page 2614, left column). Thus, the dimeric antibody taught by Pavlinkova et al [b] is a homodimer (i.e., two identical polypeptide chains; [CC49 $scFv]_2$) comprising a plurality of monomeric subunits that non-covalently associate (interpreted as two identical polypeptide chains that noncovalently associate) and the CC49 $(scFv)_2$ is modified and has at least a portion of one constant region domain omitted (i.e., domain

deleted) and lacks a CH2 domain. Pavlinkova et al [b] teach that the CC49 $(scFv)_2$ is labeled with ^{125}I or ^{131}I (see page 2614, left column).

15. Claims 29-34 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Mezes et al (WO 94/13806, 23 June 1994).

The claims and their interpretation have been described supra.

Mezes et al teach dimeric CC49 scFvs comprising a plurality of monomeric subunits that are noncovalently associated (CC49 $[scFv]_2$) and the CC49 $scFv_2$ binds the TAG-72 tumor antigen (see entire document, particularly Figure 1, abstract and pages 5 and 10-11). Thus, the dimeric antibody taught by Mezes et al is a homodimer (i.e., two identical polypeptide chains; [CC49 scFv]$_2$) comprising a plurality of monomeric subunits that noncovalently associate (interpreted as two identical polypeptide chains that noncovalently associate) and the CC49 $(scFv)_2$ is modified and has at least a portion of one constant region domain omitted (i.e., domain deleted) and lacks a CH2 domain.

16. Claims 29-33 and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Slavin-Chiorini et al (International Journal of Cancer, 53:97-103, 1993).

Claims 29-33 and 36-40 are interpreted as being drawn to a dimeric antibody comprising a plurality of monomeric subunits that are non-covalently associated, wherein the dimeric antibody is a CH2 domain deleted dimeric antibody, and binds the TAG-72 tumor antigen and the antibody is labeled (i.e., linked or conjugated) with a

radioisotope. For this rejection, the phrase "monomeric subunit comprises a modified antibody" is interpreted as a VH domain (i.e., monomeric subunit) that comprises a modified antibody (i.e., B72.3ΔC_H2). Further, the phrase "monomeric subunit(s)" is interpreted as VH and VL domains (i.e., not the entire VH and VL polypeptide chains).

Slavin-Chiorini et al teaches a CH2 domain deleted dimeric antibody (B72.3ΔC_H2) that binds the TAG-72 tumor associated antigen (see abstract, page 97 and Figure 1). For this rejection the plurality monomeric subunits that are non-covalently associated are interpreted as VH and VL domains, which are non-covalently associated (see Figure 1) and the dimeric antibody is interpreted as comprising at least one modified monomeric subunit. Thus, the dimeric antibody taught by Slavin-Chiorini et al is a comprises a plurality of monomeric subunits (VH and VL domains) that are noncovalently associated and the B72.3ΔC_H2 has at least a portion of one constant region domain omitted (i.e., CH2 domain deleted) (i.e., at least one monomeric subunit (VH) is modified). Slavin-Chiorini et al teach that the B72.3ΔC_H2 is labeled with ^{125}I or ^{131}I (see page 99, left column).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 20-34 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goel et al [a] (Cancer Research, 60:6964-6971, December 15, 2000, Ids reference XR) or Goel et al [b] (Journal of Biochemistry, 127:829-836, May 2000).

Claims 29-34 and 36-40 and their interpretations have been described supra (see item #10 above). Claims 20-28 are drawn to a kit comprising a dimeric antibody, a label or an insert indicating that said dimeric antibody may be used to treat a mammal suffering from or predisposed to a disorder, wherein the dimeric antibody comprises a plurality of monomeric subunits that are non-covalently associated, and the dimeric

antibody is a CH2 domain deleted dimeric antibody, and is a homodimer or a heterodimer. For this rejection, the term "homodimer" is interpreted as two identical polypeptide chains and the term "heterodimer" is interpreted as the two identical polypeptide chains, each having different domains (i.e., VH and VL). For this rejection the intended use of the kit for the treatment of a mammal suffering from or predisposed to a disorder is given no patentable weight. Also, the printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new*. If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed antibody. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Thus the instructions for use included in a kit or article manufacture

constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product.

Goel et al [a] have been described supra. Goel et al [a] do not specifically teach a kit comprising the tetravalent scFv formed by the noncovalent association of covalent dimer $sc(Fv)_2$ that binds the TAG-72 tumor associated antigen.

Goel et al [b] have been described supra. Goel et al [b] do not specifically teach a kit comprising the noncovalent dimer CC49 ($[scFv]_2$-His_6) that binds the TAG-72 tumor associated antigen.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claim 20-34 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al [a] (The Journal of Nuclear Medicine, 40(9):1536-1546, September 1999) or Pavlinkova et al [b] (Clinical Cancer Research, 5:2613-2619, September 1999).

The claims and their interpretations have been described supra. For this rejection the intended use of the kit for the treatment of a mammal suffering from or predisposed to a disorder is given no patentable weight. Also, the printed matter on a

label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed antibody. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product.

Pavlinkova et al [a] has been described supra. Pavlinkova et al [a] do not specifically teach a kit comprising the CC49 noncovalent dimer (CC49 $[scFv]_2$) that binds the TAG-72 tumor antigen.

Pavlinkova et al [b] has been described supra. Pavlinkova et al [b] do not specifically teach a kit comprising the CC49 noncovalent dimer (CC49 $[scFv]_2$) that binds the TAG-72 tumor antigen.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. Claim 20-34 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mezes et al (WO 94/13806, 23 June 1994) in view of Anderson et al (U.S. Patent 6,348,581, 2/18/1998).

The claims and their interpretation have been described supra.

Mezes et al has been described supra. Mezes et al also teach that compared to larger antibody fragments or entire antibody molecules, dimeric antibodies (i.e., multivalent single-chain antibodies) reach their target tissue more rapidly and are cleared more quickly from the body and for diagnostic and therapeutic uses, the dimeric antibodies can be conjugated with an appropriate imaging or therapeutic agent (see page 7, lines 20-37). Mezes et al do not specifically teach labeling the dimeric antibody with a radioisotope or kits comprising the dimeric antibody. These deficiencies are made up for in the teachings of Anderson et al.

Anderson et al teach radiolabeled CC49 for the treatment or diagnosis of cancer and radiolabeled CC49 has been reported to exhibit excellent tumor localization in several ongoing clinical trials (see entire document, particularly, column 2, lines 16-30 and columns 15-16). Anderson et al teach that suitable radionuclides include ^{90}Y, ^{131}I, ^{111}In and ^{125}I (see column 15, line 30). Anderson et al also teaches kits comprising the CC49 antibodies and instructions for using the CC49 antibody (see column 14, lines 46-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have radiolabeled the dimeric CC49 antibody taught by Mezes et al and to have placed the dimeric CC49 antibody in a kit for the advantages of convenience and economy in view of the teachings of Anderson et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have radiolabeled the dimeric CC49 antibody taught by Mezes et al and to have placed the dimeric CC49 antibody in a kit for the advantages of convenience and economy in view of the teachings of Anderson et al because Mezes et al teach a dimeric CC49 antibody that binds the TAG-72 tumor associated antigen and compared to larger antibody fragments or entire antibody molecules dimeric antibodies (i.e., multivalent single-chain antibodies) reach their target tissue more rapidly and are cleared more quickly from the body and for diagnostic and therapeutic uses, the dimeric antibodies can be conjugated with an appropriate imaging or therapeutic agent and Anderson et al teach radionuclides such ^{90}Y, ^{131}I, ^{111}In and ^{125}I that can be conjugated to the CC49 antibody for the treatment or diagnosis of cancer as

well as kits comprising the CC49 antibody and instructions for using the CC49 antibody. Therefore, it would have been obvious to the skilled artisan at the time the invention was made to have labeled the dimeric antibody taught by Mezes et al with the radionuclides taught by Anderson et al for therapeutic benefit of tumors. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have radiolabeled the dimeric CC49 antibody taught by Mezes et al and to have placed the dimeric CC49 antibody in a kit for the advantages of convenience and economy in view of the teachings of Anderson et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

21. Claims 20-26, 28-33 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slavin-Chiorini et al (International Journal of Cancer, 53:97-103, 1993).

The claims and their interpretation have been described supra. For this rejection the intended use of the kit for the treatment of a mammal suffering from or predisposed to a disorder is given no patentable weight. Also, the printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is

concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed antibody. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture. Intended use does not impart patentable weight to a product.

Slavin-Chiorini et al has been described supra. Slavin-Chiorini et al does not specifically teach a kit comprising the CH2 domain deleted dimeric antibody (B72.3ΔC_H2) that binds the TAG-72 tumor associated antigen.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
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LARRY R. HELMS, PH.D
PRIMARY EXAMINER